Prevalence of reduced bone mineral density in patients with anti-neutrophil cytoplasmic antibodies associated vasculitis and the role of immunosuppressive therapy; a cross- sectional study

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Abstract

Antineutrophil cytoplasmic antibody associated vasculitis (AAV) is a relapsing-remitting disease, which is treated with corticosteroids (CS) in combination with cyclophosphamide. One of the major side-effects of this treatment is osteoporosis which may result in the increased occurrence of fractures. In the present study, we measured the prevalence of reduced bone mineral density (BMD) in a cross-sectional cohort of patients and correlated BMD findings with cumulative doses of CS and / or cyclophosphamide. BMD was measured by dual energy X-ray absorptiometry (DEXA) of the lumbar spine, the radius and the proximal femur between January 1998 and December 1999. Cumulative doses of CS and cyclophosphamide were calculated by chart review. Ninety-nine consecutive patients (48 males; 51 females) aged 55 ± 16 years (mean ± SD) were studied 50 months (median, range 0-400) after a diagnosis of AAV had been made. Sixty-nine patients were treated with 10.7 g (median cumulative dose, range: 0.4-67.2) of CS, and 88 patients were treated with 34.1 g (median cumulative dose, range: 0.8-324.3) of cyclophosphamide. Fifty-seven percent of the patients had osteopenia (T-score: -1 to -2.5 SD), and 21% had osteoporosis (T-score: <-2.5 SD) at least at one site. Thirty-four of 37 (92%) post-menopausal women, 9 of 14 (64%) of pre-menopausal women, and 34 of 48 (71%) male patients had either osteopenia or osteoporosis. The mean age and sex adjusted BMD (Z-score) of the proximal femur in male patients was found to be significantly lower than zero. Cumulative dose of CS therapy showed an inverse relation with Z-scores at the lumbar spine (P = 0.035) and the proximal femur (P = 0.011). Cumulative dose of cyclophosphamide was not correlated with Z-scores. Osteopenia and osteoporosis are frequently observed in patients with AAV. However, only in males the mean Z-score is significantly lower than zero. Cumulative dose of CS therapy is significantly associated with bone loss at the spine and femur.

Introduction

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis affect people of all ages but is most common in older adults in their 50s and 60s, and it affects men and women equally. Treatment with high dose corticosteroids (CS) and cyclophosphamide induces disease remission in more than 80-90% of patients with ANCA associated vasculitides. Relapses, however, are frequently observed in these forms of vasculitis and treatment in such cases has to be intensified or reinstituted (Gaskin et al., 1992). As a result patients are exposed to high cumulative doses of CS and cytotoxic agents. The effect of long-term CS use on BMD has been extensively studied in various diseases (i.e. asthma, rheumatoid arthritis, connective tissue disease, and systemic lupus erythematosus). Long-term administration of CS may result in osteoporosis by inhibition of bone formation, enhancement of bone resorption, inhibition of intestinal calcium absorption, and increase of renal excretion of

calcium, but also indirectly by altering different hormonal axes and protein metabolism (Lukert et al., 1990). This effect is related to duration of therapy, the daily dose and to the total cumulative dose (Dykman et al., 1985; Reid et al., 1990; Kipen et al., 1999). Patients studied in these studies are, however, in several respect different from patients with ANCA associated vasculitis. In ANCA associated vasculitis, males and females are equally affected, there usually is a late onset of the disease, and mobility is usually only temporarily impaired. Patients with ANCA associated vasculitis are additionally exposed to cyclophosphamide which may lead to accelerated bone loss due to diminished gonadal function (Riggs et al., 1983). Furthermore, many of these patients suffer from impaired renal function which may lead to bone abnormalities and an increased prevalence of fractures (Lindberg et al., 1999).
The reported incidence of fractures in ANCA associated vasculitis ranges between 3-15% of the patients (Hoffman et al., 1992; Guillevin et al., 1997; Guillevin et al., 1999). The effect of immunosuppressive treatment on BMD in ANCA associated vasculitis has not been studied so far.
The aim of the present study is to determine the prevalence of reduced BMD in a large patient cohort of ANCA-associated vasculitis. BMD was measured by dual energy X-ray absorptiometry (DEXA) of the lumbar spine, the proximal femur, and the radius in consecutive patients with ANCA associated vasculitis who were seen at our outpatients clinic. Furthermore, we analyzed whether the occurrence of reduced BMD was correlated with cumulative doses of CS and/or cyclophosphamide, renal function, calcium intake, number of disease relapses and disease duration.

Patients and methods

Study design

Inclusion: Patients who were under regular follow-up at the vasculitis outpatient clinic, University Hospital Groningen, the Netherlands and visited the clinic between January 1998 and December 1999 were asked to participate in the current study. All patients were classified according to the Chapel Hill Consensus Conference on nomenclature of systemic vasculitides (Jennette et al., 1994). Eligibility required the (historical) presence of ANCA directed against either proteinase 3 (PR3) or myeloperoxidase (MPO). Age younger than 16 years or pregnancy were exclusion criteria.
Collected data included age, sex, weight, height, estimated dietary calcium intake, menopausal state, creatinine clearance (ml/min), and hormonal substitution status. Disease variables that were collected included diagnosis, ANCA specificity (PR3 or MPO) and duration of disease calculated from the time of diagnosis. Furthermore, cumulative doses of CS and cyclophosphamide were calculated from review of medical records between the date

of diagnosis and the date the DEXA was performed. Current dose of CS, duration of CS and cyclophosphamide therapy, and previous fractures were also recorded.
Treatment: Patients were treated with CS, cyclophosphamide and/or azathioprine with or without pulses of methyl prednisolone according to our standard protocol for ANCA associated glomerulonephritis (Franssen et al., 1998). During high-dose CS treatment, all patients received calcium carbonate combined with alphacalcidol or dihydrotachysterol therapy. During clinical relapse, therapy with CS and cyclophosphamide was restarted or increased.

Measurement of BMD

BMD of the proximal femur, lumbar spine and radius were measured by DEXA using a Hologic QDR 1000 or a Hologic QDR 4500 apparatus (Waltham, MA). Both machines were calibrated daily using the same quality assurance phantom. The coefficient of variation of the QDR 1000 and QDR 4500 scanners are 1.2% and 1.0%, respectively, for the spine, 1.5% and 1.1%, respectively, for the hip and 1.0% and 1.0%, respectively, for the radius using the Hologic phantoms. The lumbar spine was measured from L1 to L4. Further measures included the midshaft (one-third of the way up) radius and the proximal femur (femoral neck, greater trochanter and Ward's triangle). One subject did not have proximal femur BMD measurement and 4 subjects did not have radius measurement. All scans were performed between January 1998 and December 1999.
BMD as measured by DEXA is expressed in g/cm^2 and converted to T- and Z-scores. Z-score compares the patient's observed BMD with an expected value from the entire population for a person of the same age and gender (irrespective of weight). The T-score compares the patient's observed BMD with the normal value for a young adult aged 25-29 of the same gender. These normal values were from the National Health and Nutrition Examination Survey (NHANES) and based on a large reference population database from age and sex matched controls supplied by the manufacturer (Hologic Corp.). A T-score below minus 2.5 standard deviation (SD) was defined as osteoporosis and a T-score between minus 1 and minus 2.5 SD was defined as osteopenia according to the World Health Organization (WHO) criteria (Kanis et al., 1994). The study was approved by the human research ethics commitee of the University Hospital Groningen.

Statistical methods

Demographic and clinical characteristics were compared using the Fischer's exact test for categorical quantities, and the Mann-Whitney test for continuous quantities were used when appropriate. Scattergrams of BMD were generated using GraphPad Prism^{TM}. Ninety-five percent confidence intervals (unequal distribution) of mean age and sex adjusted BMD (Z-

score) were calculated. Univariate associations of clinical and demographic characteristics with age and sex adjusted BMD (Z-score) were evaluated using Pearson correlation coefficients for continuous quantities. Multivariate associations of clinical (disease duration, number of disease episodes, calcium intake, cumulative dose of CS / cyclophosphamide, renal function, ANCA specificity) and demographic characteristics (age, body mass index) with age and sex adjusted BMD (Z-score) as the dependent variable were evaluated with multiple linear regression analysis (SPSS^{TM} Software Version 9.0). A two-sided p-value <0.05 was considered to indicate statistical significance.

Table 1 Descriptive characteristics of the study population at entry (Median [range])

Characteristics	**Male**	**Female**	
		Pre-menopausal	Post-menopausal
n.	*48*	*14*	*37*
Age (y)	56 (23 – 81)	30 (19 – 48)	61 (36 – 85)
Cumulative organ involvement at time of DEXA, n (%)			
Ear, nose and/or throat	42 (88)	11 (79)	31 (84)
Lungs	29 (60)	8 (57)	17 (46)
Kidneys	33 (73)	9 (64)	26 (70)
Eyes	11 (23)	3 (21)	12 (32)
Skin	20 (42)	1 (7)	12 (32)
Joints	34 (71)	10 (71)	33 (89)
Nervous system	16 (33)	6 (43)	17 (46)
Disease duration (mo)	47 (7 – 400)	55 (20 – 174)	54 (0 – 344)
Nr. of previous relapses	1 (0 – 4)	1 (0 – 5)	0 (0 – 6)
Antigenicity (PR3/MPO)	36/12	7/7	29/8
Body mass index	26 (17 - 31)	22 (18 - 36)	25 (16 - 36)
Creatinine clearance (ml/min)	75 (13 - 156)	59 (50 - 106)	57 (12 - 92)
Corticosteroids (CS) use			
Ever used	47/48	13/14	36/37
Total dose, g [a]	11.4 (4.1 – 43.1)	10.9 (4.7 – 38.5)	10.1 (0.4 – 67.2)
Therapy duration (mo) [a]	19 (6 – 74)	22 (8 – 119)	22 (0 – 149)
Fractures	3 (6%)	0	5 (14%)

PR3 = proteinase 3; MPO = myeloperoxidase; Body mass index = weight / lenght^2.

[a] Data refer to CS users only (= prednisolone-equivalent dose)

Results

Ninety-nine consecutive patients (48 male / 51 female) with a mean (SD) age of 55 (16) years were studied (response rate 100%). The characteristics of the study participants are displayed in Table 1. Eighty patients were classified as Wegener's granulomatosis, 6 as Churg-Strauss syndrome, 11 as microscopic polyangiitis, and 2 as idiopathic necrotizing crescentic glomerulonephritis. Eighty-eight patients had been treated with CS and cyclophosphamide. Forty-five of these patients had received additional azathioprine therapy. Due to persistence of disease, 1 of these patients received additional mycophenolate-mofetil, and methotrexate therapy. Eleven patients did not receive cyclophosphamide. Four patients had been treated with CS and azathioprine, 1 patient with CS and methotrexate, and 3 patients with CS only. Additionally, 3 patients with loco-regional Wegener's granulomatosis received co-trimoxazole only without immunosuppressive medication. Twenty out of 96 patients who had been treated with CS had received additional pulses of methyl prednisolone. The time between start of therapy at diagnosis and BMD measurement was 50 months (median, range: 0 - 400) prior to the DEXA. Cumulative doses were calculated in all patients. The cumulative dose of CS (oral and intravenous pulses, prednisolone-equivalent dose) in CS users (n = 96) was 10.7 g (median, range: 0.4 - 67.2) (less than 10 g; n = 43, more than 10 g; n = 53), and the cumulative dose of cyclophosphamide in cyclophosphamide users (n = 88) was 34.1 g (median, range: 0.8 - 324.3).

Ten women were currently receiving oral anti-conceptive medication, 5 postmenopausal women were currently receiving hormone replacement therapy. Finally, 2 men had decreased testosterone levels, probably due to cyclophosphamide-induced hypogonadism and were therefore currently receiving intra muscular injections of testosterone. The median (range) estimated dietary calcium intake (without calcium supplements) was 920 (250 - 1640) mg for men, 945 (250 - 1640) mg for premenopausal women and 1025 (250 - 1775) mg for postmenopausal women, and with calcium supplements 1265 (675 - 2615) mg for men, 945 (250 - 1640) mg for premenopausal women and 1263 (250 - 2825) mg for postmenopausal women. Seventeen patients (17%) were currently receiving alphacalcidol or dihydrotachysterol therapy, and 7 (7%) were currently receiving biphosphonates.

X-rays were performed when fractures were suspected. Among 7 participants fractures had been documented on X-ray analysis during the course of disease. These included fractures of the vertebrae (n = 3), femur (n = 2) and the radius / ulna (n = 2). Fractures of the vertebrae had occurred spontaneous one elderly male patient with osteopenia, and two patients (1 male, 1 female) with a normal BMD-value of the lumbar spine. Both fractures of the femur occurred after a fall: one in an elderly female patient with osteoporosis, and one in an elderly male patient with osteopenia of the proximal femur. Both fractures of the radius / ulna occurred after a fall in two middle-aged female patients with normal BMD of the radius. Among 1 elderly female participant with osteoporosis fractures of the vertebrae had already been documented on X-ray analysis prior to diagnosis and treatment.

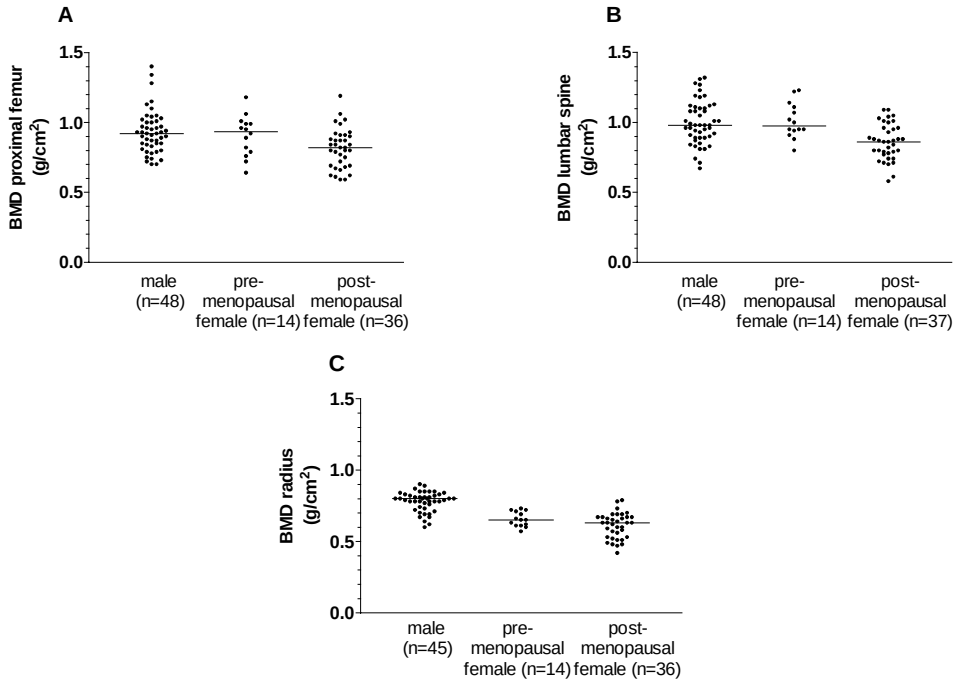

Figure 1 Scattergrams of levels of bone mineral density (BMD) (g/cm^2) of the proximal femur (A), lumbar spine (B) and the radius (C) in men, premenopausal women, and postmenopausal women with ANCA associated vasculitis. Horizontal lines indicate median value.

The median (range) BMD of the lumbar spine was 0.95 (0.58 – 1.32) g/cm^2, proximal femur 0.88 (0.59 – 1.40) g/cm^2 and radius 0.69 (0.42 – 0.90) g/cm^2 (Figure 1A-C)(Table 2). The median (range) young adult BMD (T-score) of the lumbar spine was -1.2 (-3.8 to 2.8) SD, proximal femur -0.8 (-2.9 to 2.4) SD and radius -0.7 (-4.6 to 1.5) SD (Figure 2A-C)(Table 2). In 34 out of 48 male patients (71%) BMD of either the lumbar spine, proximal femur and/or radius is considered to be low (T-score: below -1.0 SD) (premenopausal women 9 / 14 (64%), postmenopausal women 34 / 37 (92%)). Osteoporosis (T-score: <-2.5 SD) is present in 7 out of 48 male patients (15%) at either the lumbar spine, proximal femur and/or radius (premenopausal women 0 / 14 (0%), postmenopausal women 14 / 37 (38%)). Overall, 21 out of 99 (21%) of the patients had BMD values indicating osteoporosis at least at one site, 56 out of 99 (57%) patients had osteopenia at least at one site, and 22 out of 99 (22%) patients had normal BMD values at all three sites. The median (range) age and sex adjusted BMD (Z scores) of the lumbar spine was -0.2 (-3.5 to 2.9) SD, proximal femur -0.2 (-2.4 to 3.3) SD and radius 0.1 (-2.4 to 3.6) SD (Figure 3A-C)(Table 2). The mean Z-score of the proximal femur in male patients is significantly lower than zero. The mean Z-score of the lumbar spine and the radius in men, and the mean Z-score of the lumbar spine, the proximal femur, and the radius in pre- / post- menopausal women was not significantly lower than zero.

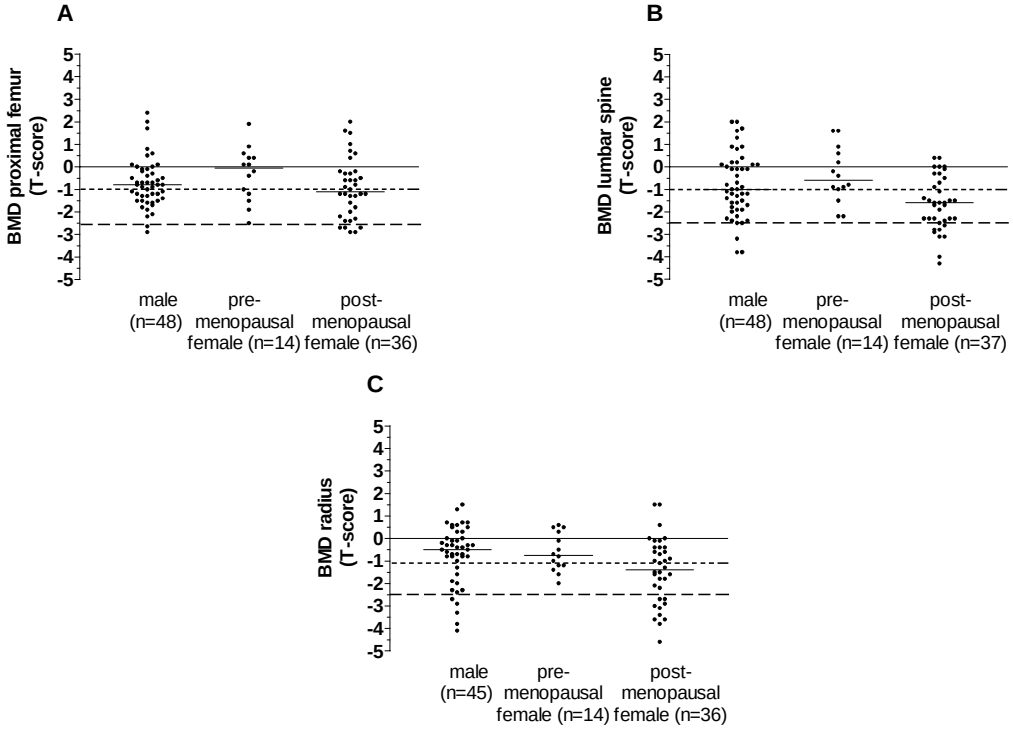

Figure 2 Scattergrams of levels of bone mineral density (BMD) (young adult T-score) of the proximal femur (A), lumbar spine (B) and the radius (C) in men, premenopausal women, and postmenopausal women with ANCA associated vasculitis. Horizontal lines indicate median value.

The result of univariate analyses of demographic and clinical characteristics with Z-scores of the lumbar spine, proximal femur and radius are shown in Table 3. Low body mass index (weight / lenght^2) is significantly associated with reduced Z-scores of the proximal femur and the radius. Other variables like disease duration and previous relapses, renal function, gender, calcium intake, and ANCA specificity were not significantly related to Z-scores.

Univariate analyses of the cumulative dose of immunosuppressive medication with Z-scores are shown in Table 4. The cumulative dose of CS is significantly associated with reduced Z-scores of the lumbar spine. The cumulative dose and the duration of cyclophosphamide are not significantly correlated with Z-scores.

Using multivariate analysis, the Z-score at the proximal femur correlated significantly and independently with body mass index (coefficient 0.103 per kg/m^2; P = 0.002), the cumulative dose of CS (coefficient -0.035 per g CS; P = 0.011), and renal function (coefficient 0.008 per ml / min; P = 0.032). The Z-score at the lumbar spine only correlated significantly with the cumulative dose of CS (coefficient -0.002 per g CS; P = 0.035), while the Z-score at the radius was correlated with body mass index only (coefficient 0.084 per kg/m^2; P = 0.01). In none of the multivariate analyses an independent association between Z-score at any of the sites with disease duration, number of disease episodes, calciumintake, or cumulative dose of cyclophosphamide was found.

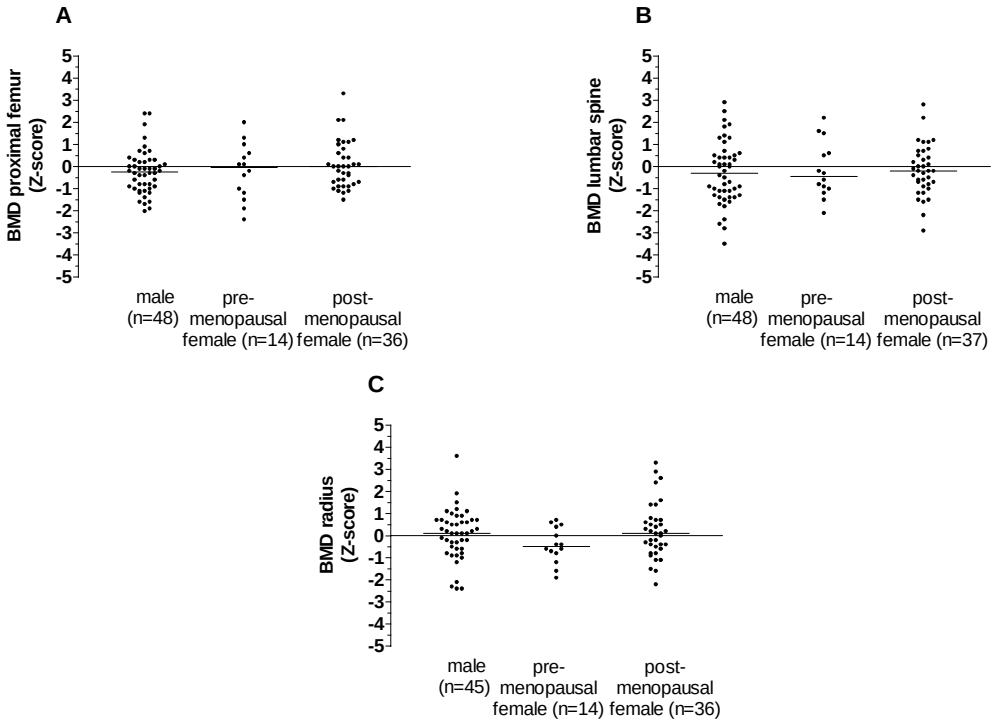

Figure 3 Scattergrams of levels of bone mineral density (BMD) (age and sex matched Z-score) of the proximal femur (A), lumbar spine (B) and the radius (C) in men, premenopausal women, and postmenopausal women with ANCA associated vasculitis. Horizontal lines indicate median value.

Table 2. Bone mineral density (Median [range])

Characteristics	**Male**	**Female**	
		Pre-menopausal	Post-menopausal
BMD lumbar spine *n.*	*48*	*14*	*37*
g/cm^2	0.98 (0.67 to 1.32)	0.98 (0.80 to 1.23)	0.86 (0.58 to 1.09)
T-score (SD)	-1.0 (-3.8 to 2.0)	-0.6 (-2.2 to 1.6)	-1.6(-4.3 to 0.4)
Z score (SD)	-0.35 (-0.68, 0.15)	-0.5 (-2.1 to 2.2)	0.2 (-2.9 to 2.8)
BMD proximal femur *n.*	*48*	*14*	*36*
g/cm^2	0.92 (0.70 to 1.40)	0.94 (0.64 to 1.18)	0.82 (0.59 to 1.19)
T-score (SD)	-0.8 (-2.9 to 2.4)	-0.1 (-2.5 to 1.9)	-1.1(-2.9 to 2.0)
Z score (SD)	-0.3 (-2.0 to 2.4)	-0.1 (-2.4 to 2.0)	0.0 (-1.5 to 3.3)
BMD radius *n.*	*45*	*14*	*36*
g/cm^2	0.80 (0.60 to 0.90)	0.65 (0.5 to 0.73)	0.63 (0.42 to 0.79)
T-score (SD)	-0.5 (-4.1 to 1.5)	-0.8 (-2.0 to 0.6)	-1.4 (-4.6 to 1.5)
Z score (SD)	0.1 (-2.4 to 3.6)	-0.5 (-1.9 to 0.7)	0.1 (-2.2 to 3.3)

T-score = young adult bone mineral density; Z-score = age and sex adjusted bone mineral density; SD = standard deviation.

Table 3 Univariate relationship of demographic and clinical characteristics with age and sex adjusted bone mineral density (Z score) (Mean [Standard Deviation])

	Lumbar Spine		Proximal femur		Radius	
	Correlation	*p*	*Correlation*	*p*	*Correlation*	*p*
Age (y)	0.11	0.27	0.07	0.50	0.19	0.06
Body mass index	0.12	0.27	**0.53**	**<0.0001***	**0.26**	**0.01***
Disease duration (mo)	-0.05	0.64	0.07	0.49	0.02	0.86
Nr. of previous relapses	-0.13	0.19	-0.09	0.36	0.11	0.27
Creatinine clearance (ml/min)	0.02	0.88	0.19	0.07	0.09	0.40
	Z score (SD)	*p*	*Z score (SD)*	*p*	*Z score (SD)*	*p*
Gender						
Male	-0.3 (1.4)	0.59	-0.3 (1.0)	0.27	0.0 (1.1)	0.48
Female	-0.2 (1.2)		0.0 (1.1)		0.0 (1.2)	
Antigenicity						
MPO-ANCA	-0.3 (1.4)	0.96	-0.3 (0.9)	0.42	-0.3 (0.9)	0.11
PR3-ANCA	-0.2 (1.2)		-0.1 (1.1)		0.2 (1.2)	
Corticoseroid (CS) use[a]						
less than 10 g CS	0.2 (1.2)	**0.01***	-0.1 (0.9)	0.86	0.0 (1.1)	0.81
more than 10 g CS	-0.5 (1.2)		-0.2 (1.2)		0.0 (1.2)	

PR3 = proteinase 3; MPO = myeloperoxidase; ANCA = anti-neutrophil cytoplasmic antibodies; SD = standard deviation; ∗ = statistically significant, P < 0.05 compared to normal values.

[a] Data refer to CS users only (= prednisolone-equivalent dose)

Table 4 Dose response relationship of immunosuppressive drugs related variables with age and sex adjusted bone mineral density (Z score) of the lumbar spine, proximal femur and radius

	Lumbar Spine		Proximal femur		Radius	
	Correlation	*p*	*Correlation*	*p*	*Correlation*	*p*
Corticosteroids (CS)						
Total dose (g)	**-0.22**	**0.03***	-0.191	0.07	0.01	0.90
Therapy duration (mo)	-0.17	0.11	-0.167	0.11	0.07	0.54
Dose at DEXA (mg/day)	-0.01	0.93	-0.072	0.49	0.08	0.45
Recovery since last CS (mo) [a]	0.13	0.22	0.191	0.07	-0.18	0.10
Cyclophosphamide						
Total dose (g)	-0.13	0.20	-0.059	0.57	0.05	0.61
Therapy duration (mo)	-0.12	0.24	-0.035	0.74	0.03	0.76

DEXA = dual energy X-ray absorptiometry; ∗ = statistically significant, P < 0.05 compared to normal values.

[a] Recovery data refer to CS users only (prednisolone-equivalent dose)

Discussion

We studied a group of 99 consecutive patients with ANCA associated vasculitis to determine the prevalence of reduced BMD as measured by DEXA. All patients asked to pertain in the study agreed. There was a high prevalence of osteoporosis and osteopenia in this patient cohort. Overall, 21 out of 99 (21%) of the patients had BMD values indicating osteoporosis as defined by the WHO criteria (BMD T-score: <-2.5 SD) and 56 out of 99 (57%) patients had osteopenia (WHO; BMD T-score: -1 SD to -2.5 SD) at least at one site. In 22 out of 99 (22%) patients normal BMD (WHO; BMD T-score >-1.0 SD) values were measured at all three sites. Remarkably, The mean age and sex adjusted BMD (Z-score) was significantly lower than zero in male patients only. Although osteopenia frequently exists in premenopausal female patients, and osteopenia / osteoporosis are common in postmenopausal female patients, Z-scores did not differ significantly from zero.

Our second finding was the positive correlation between cumulative dose of CS and reduced Z-scores of the lumbar spine (predominantly trabecular bone) and proximal femur (mixed cortical and trabecular bone). This finding is in line with results of previous studies in patients with various diseases receiving long-term CS treatment (Reid et al., 1990; Kipen et al., 1999). In contrast to *Dykman et al* (Dykman et al., 1985), we did observe a correlation between cumulative dose of CS and Z-scores of the mid-shaft radius (predominantly cortical bone). Trabecular bone is known to be more sensitive to CS compared to cortical bone (Reid, 1989). Cyclophosphamide therapy was not related to Z-scores.

However, other factors than CS result in bone loss in AAV. Disease related factors like renal failure, inflammatory process, impaired mobility due to neurological, muscle, ocular and/or ocular involvement may also account to bone loss. Multivariate analysis revealed impaired renal function and low body mass index as additional risk factors for reduced Z-scores in patients with AAV. The data did not further identify groups of patients who lose bone mass disproportionately. Disease duration, gender, calcium intake, ANCA specificity, or previous relapses necessitating resumption or intensification of immunosuppressive treatment seemed to have no impact on Z-scores.

An inverse relation between BMD and risk of fracture has been found in subjects with osteopenia (Ross et al., 1991). We found fractures in 8% of our patients. This finding is in line with the reported incidence of fractures of 3-15% in previous studies (Kipen et al., 1999; Hoffman et al., 1992; Guillevin et al., 1997; Guillevin et al., 1999). The reported incidence of fractures in patients receiving long-term steroid treatment for other diseases such as asthma has been found to be as high as 30-50% (Adinoff et al., 1983).

A limitation of our study was that X-rays were not routinely performed. Because vertebral fractures may be asymptomatic, the fracture rate in our patients may be underestimated since their prevalence can only be determined from radiological surveys. Another limitation of the study is its cross-sectional nature and hence variable disease duration and difference in CS usage. Furthermore, the number of patients studied is relative small and no data on

biochemical and hormonal parameters possibly relevant to reduced BMD in patients with AAV are available. It is therefore remarkable that we found a mean Z-score which was significantly lower than zero in men. Relatively few attention has been given to CS-induced osteoporosis in men. In line with our findings, *Reid et al* reported that the rate of change in BMD during CS therapy was unrelated to gender (Reid et al., 1990). In their study, however, male BMD values were not compared to age and sex matched controls.

Is additional treatment needed in patients with ANCA associated vasculitis? In recent years new promising drugs, such as biphosphonates bisphosphonate (e.g., etidronate, alendronate, risedronate) have been shown to prevent CS induced osteoporosis (Adachi et al., 1997; Saag et al., 1998; Cohen et al., 1999). Calcitriol, calcitonin,parathyroid hormone and fluoride may have roles as adjunctive therapies but documentation of their efficacy is less satisfactory (Luengo et al., 1990; Healey et al., 1996; Lane et al., 1998). Since male patients have a mean Z-score which is significantly lower than zero, additional treatment may be beneficial in these patients. The mean Z-score in postmenopausal women was not significantly lower than zero. It is, however, not known whether the correlation between BMD and fracture risk, as shown in postmenopausal osteoporosis, is similar in steroid treated patients. Patients treated with CS may have abnormal bone quality, and BMD alone cannot be used to predict the risk of fractures in these patients since these patients may have a higher susceptibility for fractures (Peel et al., 1994). From previous studies it is known that hormonal replacement therapy is recommended in postmenopausal women since menopausal status is considered as a risk factor for bone loss and fractures (Dykman et al., 1985; Lukert et al., 1994; Carbonare et al., 2001). However, in the present study bone loss in women was not evident.

From the present study it is clear that the daily calcium intake, which is believed to be a determinant of BMD, in women was sub-optimal. The median estimated dietary calcium intake (with calcium supplements) for premenopausal (945 mg) and postmenopausal women (1263 mg) was lower than the optimal daily calcium intake of 1000 mg and 1500 mg, respectively, as recommended by the National Institutes of Health Consensus Panel (NIH) (NIH, 1994). This stresses the need for improved nutrition or calcium supplements.

In conclusion, osteoporosis and osteopenia are frequently observed in patients with ANCA associated vasculitis. The mean age and sex adjusted BMD (Z-score), however, was only significantly lower than zero in males. We found that the cumulative dose of CS therapy is a significant contributor to bone loss of the lumbar spine and proximal femur. We were not able to identify a role for cyclophosphamide therapy. As the prognosis of ANCA associated vasculitis continues to improve, the potential of reduced BMD to contribute to morbidity increases. More attention should be directed to the particular low BMD of men. This is the group that has been particularly neglected with regard to bone diseases. Additional studies are needed to demonstrate that treatment may be beneficial in these patients to reduce the prevalence of reduced BMD and/or the incidence of fractures.

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